CRP showed the veno-aortic differences. Intense L-PGDS-immunoreactivity was detected in smooth muscle cells and extracellular matrix of the coronary arteries with early atherosclerosis and in the atheromatous vein graft, but the level was faint in the native coronary artery with marked atherosclerosis. The expression profiles of L-PGDS mRNA were consistent with the immunohistochemical findings.
Conclusion: L-PGDS is actively secreted from the early atherosclerotic plaque in the coronary circulation. Serum L-PGDS is useful as a marker of coronary atherosclerosis.

10:45 a.m.

847-2 Comparative Effects of Statin and Fibrate on Nitric Oxide Bioactivity and Markers of Inflammation in Hyperlipidemia

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Background: We investigated whether most commonly used lipid-lowering therapies-statins and fibrate improve nitric oxide (NO) bioactivity and reduce serological markers of inflammation and whether these therapies-induced reduction in markers of inflammation is mediated by improvement in NO bioactivity or lipoprotein changes.
Methods: For 8 weeks, we administered simvastatin 20 mg or fenofibrate 200 mg daily to each 27 randomly selected patients with hypercholesterolemia and coronary artery disease or pure hypertriglyceridemia, respectively. Data= mean±SEM and median (25%-75%).
Results: Both therapies significantly changed lipoprotein levels from the respective baseline levels. As expected, simvastatin significantly lowered TC and LDL-C more and fenofibrate increased TG and
HDL-C more than either therapy. Simvastatin and fenofibrate significantly improved the percent flow-mediated dilator response to hyperemia (FMD) from 3.36±0.45 to 6.06±0.47 and from 5.20±0.35 to 6.38±0.33, respectively (each P<0.001), however, simvastatin significantly improved FMD and reduced plasma levels of malondialdehyde (MDA), a marker of free radical from 1.95±0.13 to 1.60±0.15 uM (P<0.01) to greater extent. Both therapies did not change plasma levels of nitrate. Simvastatin and fenofibrate significantly lowered plasma levels of TNF-α from 3.31±0.35 to 2.67±0.27 pg/ml and from 1.61±0.10 to 1.43±0.10 pg/ml (each P<0.01), respectively and serum levels of CRP from 0.59 to 0.16 (P<0.001) and from 0.17 to 0.11 (P=0.280), respectively, however, simvastatin significantly lowered CRP levels to greater extent than fenofibrate. There were significant inverse correlation between LDL cholesterol and flow-mediated dilation percent (r=-0.342, P=0.009). Of interest, there were significant inverse correlations between flow-mediated dilation percent and TNF-α levels (r=-0.293, P=0.035). However, no significant correlations between lipoprotein levels and levels of inflammation markers were determined.
Conclusions: Simvastatin and fenofibrate significantly improved NO bioactivity through different biological mechanisms on lipoproteins and markers of free radical and inflammation.

11:00 a.m.

847-3 Methionine Synthase A 2756 G/ Methylenetetrahydrofolate Reductase C 677 T Combined Polymorphisms: Either Protective or Risk Factors of Coronary Artery Disease

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Background: Case control studies evaluating the 677CT polymorphism of methylenetetrahydrofolate reductase (MTHFR) as an independent genetic risk factor of coronary artery disease have produced contradictory conclusions. The reason could be that its association to all other polymorphisms of the enzymes related to homocysteine metabolism has never been taken into account. These polymorphisms are the 1298 AC, 2756 AG and 66 AG substitutions in the genes of MTHFR, methionine synthase (MTR) and methionine synthase reductase (MTRR) respectively.
Methods: We investigated the individual and combined effects of these 4 polymorphisms and of nutritional (vitamin B6, vitamin B12, folates) and metabolic factors (cystathionine, methylmalonate, cystatine-C) relied with the plasma homocystein (t-Hcys) level in case control study including 108 patients and 130 controls.
Results: The plasma t-Hcys was higher in patients than in controls (P<001). It was also higher in MTHFR 677 TT, than in 677 CC and 677 CT, in controls, but not in patients. Cystatin-C, marker of glomerular filtration was the single independent determinant of increased t-Hcys of patients (P = 0.04), in multiple regression analysis, taking also into account folates, vitamin B6 and B12, cystationine and methylmalonic acid. The upper quartile of t-Hcys (>10.5 µmol/l) and MTR 2756 AG/GG genotype were significant independent risk factors of coronary artery disease with respective Odds ratios of 3.0 (95 % CI: 1.7-5.3, P=0.0002) and of 2.8 (95% CI: 1.3-6.0, P=0.0111). By contrast, the combination of MTHFR 677 CT/MTR 2756 AG, MTHFR 677 CC/1298 AC and MTHFR 677 CT/ 1298AA were protective, with Odd ratios of 0.13, 0.48 and 0.34, respectively.
Conclusion: MTR 2756 AG genotype considered alone is a potent risk factor of coronary artery disease while it becomes protective in association with MTHFR 677 CT genotype. Increase of t-Hcys is rather influenced by glomerular filtration than by genetic and nutritional factors. Our study illustrates the necessity to evaluate the relative risk generated by t-Hcys by considering the interaction of all genetic nutritional and metabolic potential determinants rather than by evaluating independently each one.

11:15 a.m.

847-4 Acute Increases in Methylated Arginines in Obstructive Sleep Apnea: Implications for Cardiovascular Risk

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Background: Obstructive sleep apnea (OSA) has been increasingly linked to cardiovascular diseases and endothelial dysfunction. Methylated arginines, endogenous inhibitors of nitric oxide synthase, have been implicated as a possible mechanism for endothelial dysfunction in cardiovascular diseases. We tested the hypothesis that repetitive severe hypoxemia resulting from OSA would increase serum asymmetrically methylated arginines (asymmetric dimethylarginine, ADMA, and monomethylarginine, L-NMMA).
Methods: We studied 10 men with newly diagnosed OSA who were free of other diseases, had never been treated for OSA, and were taking no medications. Measurements were made before and after 5 hours of untreated OSA, and again after 4 hours of acute continuous positive airway pressure (CPAP) treatment. We compared methylated arginine measurements in these patients to measurements obtained at similar times in 10 matched control subjects.
Results: Baseline ADMA and L-NMMA levels before sleep were similar in the OSA and control group. ADMA and L-NMMA levels increased significantly (from 13.9±0.7 to 16.1±0.5, P=0.03, and from 4.6±0.2 to 5.5±0.1 ng/ml, P=0.002, respectively) in the OSA group after 5 hours of untreated OSA. The increase in ADMA and L-NMMA was blunted by acute CPAP treatment. There was a significant correlation between Apnea-Hypopnea Index and increases in ADMA (R=0.58, P=0.0077) and L-NMMA (R=0.63, P=0.0028). In the control group, methylated arginine levels were stable throughout the night.
Conclusions: OSA is associated with acute elevation of ADMA and L-NMMA. This increase is blunted by effective CPAP treatment. Increased asymmetrically methylated arginines may be a potential mechanism to explain the association between OSA and cardiovascular disease.

11:30 a.m.

847-5 A Prospective Study of Hemoglobin A1c and Future Cardiovascular Events in Women

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Background: Available data suggest that hemoglobin A1c (HbA1c) levels may be related to cardiovascular risk in the general non-diabetic population. We sought to test this hypothesis prospectively in a cohort of women without overt cardiovascular disease.
Methods: We conducted a nested 1:2 case:control study in the Women's Health Study cohort. We identified 464 cases of incident myocardial infarction, stroke, or coronary revascularization and 928 controls who remained free of cardiovascular events at the time of case diagnosis. The mean follow-up was 7 years.
Results: 136 of the overall study population had a history of diabetes at enrollment or an overtly elevated baseline HbA1c (>6.40%) and were excluded from the primary analyses. Among women without diabetes or an elevated baseline HbA1c, baseline mean levels of HbA1c were significantly higher among future cardiovascular cases than controls (5.47% ± 0.27 vs 5.37% ± 0.22; p<0.0001). The crude relative risks (RR) of incident cardiovascular events for increasing quartiles of HbA1c were 1, 0.98, 1.33, and 2.25 (95% CI for highest vs lowest quartile 1.59-3.18). HbA1c levels were significantly correlated with several other traditional cardiovascular risk factors, including age, body mass index, systolic blood pressure, C-reactive protein, and total cholesterol: high density lipoprotein-cholesterol ratio. In fully adjusted models the predictive effect of HbA1c was attenuated and not significant (RR = 1.00 for top vs bottom quartile, 95% CI 0.65-1.54). In contrast, in the population including women with diabetes at enrollment, diabetes (RR 4.97, 95% CI 2.81-8.77) remained a strong independent determinant of cardiovascular risk in fully adjusted analyses, while HbA1c levels did not (RR = 1.11 for top vs bottom quartile, 95% CI 0.73-1.71).
Conclusion: HbA1c is associated with future cardiovascular risk among non-diabetic women, but this relationship is largely attributable to a strong correlation with other cardiovascular risk factors. In contrast, diabetes is a strong independent determinant of cardiovascular risk, even after adjustment for HbA1c levels.

11:45 a.m.

847-6 Plasma Glutathione Redox State: A Novel Marker of Oxidative Stress, Correlates With Early Atherosclerosis in Humans

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Background: Although trials of antioxidant therapy for cardiovascular disease in humans have not shown long-term benefit, there remains evidence in animals for the role of oxidative stress in the pathogenesis of atherosclerosis. The plasma redox state of glutathione (Eh GSH/GSSG) has been shown to be a novel marker of oxidative stress in humans. We hypothesized that in Eh GSH/GSSG and endothelial dysfunction would both correlate with the presence of early atherosclerosis in humans.
Methods: We evaluated brachial artery flow-mediated dilation (FMD) and common carotid artery intima media thickness (CIMT) in 40 adults with no clinical atherosclerotic disease. Plasma glutathione (GSH), oxidized glutathione (GSSG), Eh GSH/GSSG, and FMD were correlated with CIMT.
Results: There was an inverse correlation between CIMT and FMD (r = - 0.43, p- 0.005).